



General

Guideline Title

Fabry disease practice guidelines: recommendations of the National Society of Genetic Counselors.

Bibliographic Source(s)

Laney DA, Bennett RL, Clarke V, Fox A, Hopkin RJ, Johnson J, O'Rourke E, Sims K, Walter G. Fabry disease practice guidelines: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2013 Oct;22(5):555-64. [71 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Bennett RL, Hart KA, O'Rourke E, Barranger JA, Johnson J, MacDermot KD, Pastores GM, Steiner RD, Thadhani R. Fabry disease in genetic counseling practice: recommendations of the National Society of Genetic Counselors. 2002 Apr;11(2):121-46.

Recommendations

Major Recommendations

Testing and Diagnosis Recommendations

A suspicion that a patient is affected by Fabry disease is usually based on a targeted patient medical history and a detailed family history. High yield clinical and family history features are summarized in the table below. Although Fabry disease is considered highly penetrant in males and females, it can be variable in its expression.

Table. When to Consider Fabry Disease as a Diagnosis

Test ANY patient who has:

1. A family history of Fabry disease OR
2. Corneal verticillata ("whorls") on slit lamp exam

In the absence of these two factors, test patients with at least two of the features below.

1. Decreased sweating (anhidrosis or hypohidrosis)
2. Reddish-purple skin rash in the bathing trunk area (angiokeratomas)

3. Personal and/or family history of kidney failure
4. Personal or family history of "burning" or "hot" pain in the hands and feet, particularly during fevers (acroparesthesias)
5. Personal or family history of exercise, heat, or cold intolerance
6. Patients with sporadic or non-autosomal dominant (no male-to-male) transmission of unexplained cardiac hypertrophy

Diagnosis of Fabry disease is confirmed using a combination of biochemical and molecular testing (see Figure 1 in the original guideline document).

1. Fabry disease can be confirmed in males with deficiency of alpha-galactosidase A (α -gal A), most commonly measured in blood (leukocytes), and the presence of a disease causing mutation in the *GLA* gene located on Xq22.1. Although in the past low α -gal A activity has been considered sufficient for diagnosis in males, the presence of a common pseudodeficiency allele, D313Y, that results in low plasma α -gal A activity and slightly reduced leukocyte enzyme activity suggests that a diagnosis of Fabry disease should not be finalized until a disease causing *GLA* mutation is identified.
2. Measurement of α -gal A enzyme activity is not reliable for diagnosis of Fabry in females because obligate heterozygotes have variable levels of α -gal A that can overlap with enzyme levels found in healthy controls. In females confirmation of Fabry is via identification of a Fabry disease causing mutation in the *GLA* gene.
3. Biopsies of heart or kidney are not required for diagnosis in this condition, although storage patterns on biopsies may suggest a Fabry disease diagnosis in an affected individual.

Prenatal diagnosis of Fabry disease is possible using amniocytes and chorionic villi for enzymatic and molecular testing, although only molecular testing is routinely performed in the United States. Preimplantation genetic diagnosis for families with a known familial mutation is also available via assisted reproduction centers.

Newborn screening for Fabry disease is now technically possible and programs have begun in Taiwan, Missouri, Washington State, and Illinois. Other states such as New Mexico and New Jersey also have legislated beginning newborn screening for Fabry and will begin testing in the near future. The methods utilized are designed to limit false positive and negatives, but most are based on enzyme measurement which will predominantly diagnose males and a subset of affected females with low enzyme. Although not currently on the recommended panel of conditions to screen, several state legislatures have mandated screening for Fabry disease. The goals of newborn screening for Fabry disease are to diagnosis patients earlier, avoid the "diagnostic odyssey," monitor and treat patients prior to irreversible damage, and identify family members at-risk to be affected by Fabry disease. Issues surrounding the testing also relate to identification of other affected family members. Newborn screening has begun in selected states, so the issue of pediatric management and timing of initiation of enzyme replacement therapy (ERT) has expanded.

Clinical Follow-up and Intervention by Appropriate Medical Professionals

The progressive nature of Fabry disease requires at least annual evaluation and revision of management based on clinical and lab assessments by the appropriate medical professionals. Guidelines for multidisciplinary management and ERT treatment have been published for both pediatric and adult patients. In short, the following steps are recommended for any individual once a diagnosis of Fabry disease is made:

1. Referrals by appropriate medical professionals to a metabolic specialist and genetic counselor for discussion of diagnosis, recurrence risk, construction of a detailed family history, identification of other at risk family members, and development of a comprehensive monitoring and treatment plan. Contact information for medical professionals experienced in treating Fabry disease patients can be found by contacting the National Fabry Disease Foundation.
2. Baseline evaluations to be ordered by and under the supervision of appropriate medical professionals as recommended for age group include:
 - Complete blood count (CBC), platelet count, serum creatinine and blood urea nitrogen (BUN), globotriaosylceramide (GL3), thyroid studies, common thrombophilic blood coagulation disorders, and a basic metabolic chemistry panel
 - Routine urinalysis
 - 24 h urine with creatinine, glomerular filtration rate, and protein clearance
 - First morning urine measuring total protein and creatinine levels
 - Electrocardiogram (EKG)
 - 24 h Holter monitor
 - Echocardiogram and/or cardiac magnetic resonance imaging (MRI)
 - Brain MRI or head computed tomography (CT)
 - Hearing examination
 - Ophthalmologic examination
 - Pulmonary function testing
 - Depression/anxiety assessment

3. Discussion with appropriate medical professionals of treatment with ERT. Treatment practices vary widely in recommended timing of beginning ERT. The decision to initiate therapy should be determined based on the clinical judgment of the managing metabolic specialist after reviewing baseline evaluations in conjunction with the patient or patient's family in affected minors.

Genetic Counseling Recommendations

Genetic counseling specific recommendations related to issues in Fabry disease encompass a wide range of topics (see Table 2 in the original guideline document).

Specific points to examine further during sessions include:

1. Ascertaining patients' needs and concerns relating to a Fabry disease diagnosis
2. Identifying at-risk family members through construction of a detailed pedigree and diagnostic testing
3. Explaining the natural history and inheritance pattern of Fabry disease
4. Provision of pre- and post-counseling regarding genetic testing including the issue of non-paternity
5. Navigation of personal and family testing (enzyme, sequencing, duplication/deletion testing)
6. Discussions related to prenatal testing and decision making, assessing the subjects' psychosocial issues
7. Identifying appropriate support resources

Key Fabry-specific points to address during these discussion topics include:

1. The X-linked pattern of inheritance for Fabry disease and testing at-risk family members. On average, there are 5 family members diagnosed with Fabry disease for every proband. Discussion should include issues of misattributed paternity which could arise from testing. This disease should be referred to as an X-linked disorder not an "X-linked recessive disorder."
2. Clinical manifestations of Fabry disease occur in men and women. Women are not "just carriers."
3. Fabry disease is progressive and often becomes symptomatic in childhood. The average presentation age in males is 6–8 years of age and 9 years of age in females, although age of symptom onset varies from individual to individual even within the same family. Nevertheless, life threatening complications are rare in pediatric patients.
4. Types of genetic testing available and test limitations (e.g., enzyme assay can be normal in heterozygous females; the percentage of residual α -gal A enzyme activity does not correlate with clinical severity; and mutations frequently cannot predict disease severity).
5. Issues related to genetic testing for Fabry disease such as testing "healthy" minors and insurance implications.
6. Testing kidney donors, particularly family members, prior to transplant for Fabry disease
7. Reproductive options including gamete donation, prenatal diagnosis and preimplantation diagnosis.
8. Teratogenic risk of frequently used medications in Fabry disease such as Dilantin, carbamazepine (Tegretol), and angiotensin-converting-enzyme (ACE) inhibitors in pregnancy
9. Issues related to treatment compliance on a life-long infusion therapy including: transition from parent to patient directed medical care as the patient becomes an adult, insurance issues, realistic expectations of treatment efficacy, continued need for concomitant treatments and monitoring, and possible weight gain
10. Identify potential substance abuse; pain can be one of the most debilitating features of Fabry disease, and there can be problems with substance abuse as a form of self-medication.
11. Identify issues of sexuality. Men and women with Fabry disease may have concerns about body image, intimacy, and sexuality. For example, affected individuals may be embarrassed by angiokeratomas in their genital region. Chronic pain and fatigue and erectile dysfunction may also contribute to difficulties and problems with intimacy.
12. Review of management options and prevention, and referral to specialists as appropriate
13. Due to years of misdiagnosis, there can be an inherent mistrust of health professionals.
14. Discussion of the increased rate of depression, anxiety, and adaptive function disorders (ability to function in daily life and maintain relationships) seen in Fabry disease.
15. Discussion of the unique psychosocial issues in relation to Fabry disease. Overall the psychosocial issues in relation to a diagnosis of Fabry disease are similar to those associated with a diagnosis of other chronic genetic disorders (e.g., anxiety, anger, grief, denial, blame, hopelessness, and influence on self-esteem and self-identity, changed relationships with family of origin). The chronic nature of this condition can stress relationships. There is a higher rate of unemployment and suicide.

Clinical Algorithm(s)

An algorithm titled "Fabry Testing Roadmap" is provided in the original guideline document.

Scope

Disease/Condition(s)

Fabry disease

Guideline Category

Counseling

Management

Risk Assessment

Screening

Clinical Specialty

Cardiology

Dermatology

Family Practice

Gastroenterology

Internal Medicine

Medical Genetics

Nephrology

Neurology

Ophthalmology

Otolaryngology

Pediatrics

Psychology

Pulmonary Medicine

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Nurses

Physician Assistants

Physicians

Psychologists/Non-physician Behavioral Health Clinicians

Guideline Objective(s)

- To provide health care professionals with guidelines for testing, care coordination, and identification of psychosocial issues
- To facilitate a better understanding of disease treatment expert recommendations for patients with Fabry disease
- To improve the care of patients with Fabry disease by establishing a comprehensive and detailed set of recommendations for the genetic counseling and management of this population

Target Population

Individuals and families in whom the diagnosis of Fabry disease is suspected or has been confirmed

Interventions and Practices Considered

Evaluation/Screening

1. Targeted patient medical history and a detailed family history
2. Measurement of alpha-galactosidase A (α -gal A) enzyme activity in males
3. Confirmation of a Fabry disease-causing mutation in the *GLA* gene
4. Prenatal diagnosis of Fabry disease using amniocytes and chorionic villi for enzymatic and molecular testing
5. Newborn screening for Fabry disease

Management/Counseling

1. Clinical follow-up and intervention by appropriate medical professionals
2. Annual evaluation and revision of management based on clinical and lab assessment
3. Multidisciplinary management and enzyme replacement therapy
4. Genetic counseling concerning Fabry disease
 - Ascertaining patients' needs and concerns relating to a Fabry disease diagnosis
 - Identifying at-risk family members through construction of a detailed pedigree and diagnostic testing
 - Explaining the natural history and inheritance pattern of Fabry disease
 - Provision of pre- and post- counseling regarding genetic testing including the issue of non-paternity
 - Navigation of personal and family testing (enzyme, sequencing, duplication/deletion testing)
 - Discussions related to prenatal testing and decision-making, assessing the subjects' psychosocial issues
 - Identifying appropriate support resources

Major Outcomes Considered

- Diagnostic yield and reliability of biochemical and molecular testing
- Morbidity and mortality associated with Fabry disease
- Quality of life

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A PubMed search of the literature from January 2005 to April 26, 2013 revealed over 2,985 articles about Fabry disease with several updated guidelines and management articles from within and outside the United States. Specific search terms used: "Fabry disease," "Enzyme replacement therapy," "Genetic counseling," "Newborn screening," and "Lysosomal storage diseases,"

Number of Source Documents

84

Methods Used to Assess the Quality and Strength of the Evidence

Not stated

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

These recommendations are the opinions of a multicenter working group of genetic counselors, medical geneticists, and other health professionals with expertise in Fabry disease counseling, as well as representatives/founders of the two United States based Fabry disease patient advocacy groups who are themselves affected by Fabry disease. The recommendations are U.S. Preventive Task Force Class III (1989 rating scheme), and they are based on clinical experience, a review of pertinent English-language articles, and reports of expert committees.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Not stated

Description of Method of Guideline Validation

Not applicable

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are based on clinical experience, a review of pertinent English language articles, and reports of expert committees.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate testing, care coordination, and identification of psychosocial issues, and facilitation of a better understanding of disease treatment

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

- The practice guidelines of the National Society of Genetic Counselors (NSGC) are developed by members of the NSGC to assist genetic counselors and other health care providers in making decisions about appropriate management of genetic concerns, including access to and/or delivery of services. Each practice guideline focuses on a clinical or practice-based issue, and is the result of a review and analysis of current professional literature believed to be reliable. As such, information and recommendations within the NSGC practice guidelines reflect the current scientific and clinical knowledge at the time of publication, are only current as of their publication date, and are subject to change without notice as advances emerge.
- In addition, variations in practice, which take into account the needs of the individual patient and the resources and limitations unique to the institution or type of practice, may warrant approaches, treatments and/or procedures that differ from the recommendations outlined in this guideline. Therefore, these recommendations should not be construed as dictating an exclusive course of management, nor does the use of such recommendations guarantee a particular outcome. Genetic counseling practice guidelines are never intended to displace a health care provider's best medical judgment based on the clinical circumstances of a particular patient or patient population. Practice guidelines are published by NSGC for educational and informational purposes only, and NSGC does not "approve" or "endorse" any specific methods, practices, or sources of information.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Laney DA, Bennett RL, Clarke V, Fox A, Hopkin RJ, Johnson J, O'Rourke E, Sims K, Walter G. Fabry disease practice guidelines: recommendations of the National Society of Genetic Counselors. *J Genet Couns*. 2013 Oct;22(5):555-64. [71 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2002 Apr (revised 2013 Oct)

Guideline Developer(s)

National Society of Genetic Counselors - Medical Specialty Society

Source(s) of Funding

National Society of Genetic Counselors

Guideline Committee

Working Group

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Not stated

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Guideline Availability

Electronic copies: Available to subscribers from the [Journal of Genetic Counseling Web site](#) .

Availability of Companion Documents

The following is available:

- Bennett RL, French KS, Resta RG, Doyle DL. Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Couns 2008 Oct;17(5):424-33. Available to subscribers from the [Journal of Genetic Counseling Web site](#) .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on January 9, 2003. The information was verified by the guideline developer on March 11, 2003. This summary was updated by ECRI Institute on May 9, 2014. The updated information was verified by the guideline developer on June 2, 2014.

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